



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

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OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: AMDRO- Updated Quantitative Risk Assessment on a  
Chronic Toxicity/Oncogenicity Study in Female Mice.  
Caswell #642Ab.

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Summary:

The peer review committee classified Amdro as a [B2] carcinogen, hence a quantitative analysis was performed on a 78 week chronic oral toxicity/oncogenicity study in female CD-1 mice at dietary concentrations of 0, 25, 50, 100, and 200 ppm. There was a significant increase in mortality with increasing dose (trend), and both the 100 and 200 ppm dose groups had significantly higher mortality than the controls. Using female mouse lung tumors and the Weibull time-to-tumor model, the surface area corrected estimate of  $Q_1^*$  is  $1.1 \times 10^{-0}$  (mg/kg/day)<sup>-1</sup>.

Background:

Amdro was fed to 50 CD-1 mice/sex/dose level. The diet concentrations were 0, 25, 50, 100, and 200 ppm for 78 weeks. The study was conducted at International Research and Development Corporation and completed in 1982.

A peer review memo of Amdro dated April 22, 1987 classified Amdro as a category B2 carcinogen. A quantitative risk assessment was carried out in 1982 (Memo dated 10/18/82). The estimated  $Q_1^*$  was  $7.6 \times 10^{-2}$  (mg/kg/day)<sup>-1</sup> based on female mouse lung tumors. The surface area corrected human estimated  $Q_1^*$  was  $7.5 \times 10^{-1}$  (mg/kg/day)<sup>-1</sup>.

In this memo a quantitative risk assessment is conducted on female mouse lung tumor data as provided by the reviewer. Female mouse lung tumors were selected by the reviewer as the appropriate data set to conduct the quantitative risk assessment (Table 1).

Survival Analysis:

The Thomas, Breslow, Gart procedure (1977) was used to analyze the time-to-death on study data (Table 2). There was a significant increasing trend with increasing dose of Amdro ( $p < .001$ ). Both the 200 ppm dose and the 100 ppm dose had significantly more mortality than the controls ( $p < .001$  and  $p = .001$ , respectively) by both the Cox's test and the generalized K/W test.

Table 1. AMDRO - Female Mouse Lung Tumor Rates<sup>+</sup> and Cochran-Armitage Test and Fisher's Exact Test Results

Dose (ppm)	0	25	50	100	200
Adenoma	6/48 (12)	11/47 (23)	12/45 (27)	9/37 (24)	4/26 (15)
Carcinoma	2/46 (4)	4/40 (10)	6/41 (15)	4/33 (12)	
Pooled	8/48 (17)*	15/47 (32)	18/45 (40)*	13/47 (35)*	

- a/ First adenoma observed at 40 weeks in 50 ppm dose group.  
 b/ First carcinoma observed at 65 weeks in 0 ppm dose group.

+ Tumor Bearing Animals/ Animals at Risk.

Note - Significance of Trend Analysis denoted at Control.  
 Significance of pairwise comparison with control denoted at Dose level. (\* p < .05, \*\* p < .01)

Table 2. AMDRO - Male Mice Mortality Rates<sup>+</sup> and Cox or Generalized K/W Test Results

Dose (ppm)	WEEKS				TOTALS
	0-26	27-52	53-65	66-78 <sup>a</sup>	
0	0/50	3/50	2/47	7/45	12/50 (24)**
25	2/50	4/48	4/44	2/40	12/50 (24)
50	2/50	6/48	1/42	8/41	17/50 (34)
100	4/50	11/46	3/35	10/32	28/50 (56)**
200 <sup>b</sup>	11/50	23/39	1/16		35/50 (70)**

- a/ Final sacrifice was at 79 weeks.  
 b/ All animals sacrificed at 55 weeks.

+ Number of Animals Died/Number of Live Animals at the beginning of the interval.  
 ( ) Percent.

Note - The above survival tables are broken into aggregate time intervals for display purposes only.  
Significance of Trend Analysis denoted at Control.  
Significance of pairwise comparisons with control denoted at Dose level. (\* =  $p < .05$ , and \*\* =  $p < .01$ )

#### Quantitative Analysis:

Since there were survival problems and the pooled lung tumors had a significant trend, the Weibull time-to-tumor multi-stage model with a time factor to adjust for early mortality was used. The model was run for all 5 doses, 4 doses eliminating the 200 ppm dose, and 3 doses eliminating the two high doses to allow for comparison of different data sets (Table 4). To allow for comparisons of different models, the Crump multi-stage model was also run (table 5).

As can be seen from tables 4 and 5 there is little difference between the lower bound estimates for the two models. The previous estimate using the Crump model was  $Q_1^* = 7.5 \times 10^{-2}$  (mg/kg/day)<sup>-1</sup> which is slightly different from the current estimate of  $Q_1^* = 6.7 \times 10^{-2}$  (mg/kg/day)<sup>-1</sup>. This difference may be due to slight differences in the data used or an older version of the program.

Since there were survival problems the Weibull model was selected. The 3 dose data set was also chosen since the peer review committee decided that the maximum tolerated dose (MTD) was exceeded for both the 100 and 200 ppm doses. The best estimate of  $Q_1^*$  is  $8.4 \times 10^{-2}$  (mg/kg/day)<sup>-1</sup> based on extrapolation from mouse lung tumors. If we apply the surface area correction to account for species differences then the estimate of  $Q_1^*$  is  $1.1 \times 10^{-0}$  (mg/kg/day)<sup>-1</sup> assuming a 25 gram mouse and a 60 kilogram human.

Table 4. Weibull Multistage estimates from Mouse Lung Tumors

Number Doses	$Q_1^*$	MLE	DOSE (mg/kg/day) Lower Bound
5	$4.9 \times 10^{-3}$	$3.7 \times 10^{-5}$	$2.0 \times 10^{-5}$
4	$5.0 \times 10^{-2}$	$3.6 \times 10^{-5}$	$2.0 \times 10^{-5}$
3	$8.4 \times 10^{-2}$	$2.0 \times 10^{-5}$	$1.2 \times 10^{-5}$

Table 5. Crump Multistage estimates from Mouse Lung Tumors

Number Doses	Fit	$Q_1^*$	MLE	DOSE (mg/kg/day) Lower Bound
5	.007	$2.0 \times 10^{-3}$	600	$5.0 \times 10^{-4}$
4	.101	$2.4 \times 10^{-2}$	$1.1 \times 10^{-4}$	$4.2 \times 10^{-2}$
3	.606	$6.7 \times 10^{-2}$	$2.6 \times 10^{-5}$	$1.5 \times 10^{-5}$

Bibliography:

Thomas, D G, N Breslow, and J J Gart, Trend and Homogeneity Analyses of Proportions and Life Table Data, Computers and Biomedical Research 10, 373-381, 1977.

Cox, D.R. Regression Models and Life Tables (with discussion). J. Roy. Stat. Soc. Ser. B. 34, 187-220, 1972.

CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Andro (Pyrimidinone) Caswell #642AB CAS No. 67485-29-4 A.I. CODE: 118401 CFR No. 180.0	26wk feeding- dog MOEL= 0.3300 mg/kg 0.00 ppm LEL= 1.0000 mg/kg 0.00 ppm ONCO: Class B2 (TOX NOTE).	Increased absolute and relative liver weights, increased relative brain weights. Positive for oncogenicity in the rat, negative in the mouse.	PAD1 1000 OPP RFD= 0.000300 EPA RFD= 0.000300 WHO RFD 0.000000 Type:	No data gaps. 26 week dog study was accepted for chronic data requirement. However UF of 1000 used since dog is most sens. spec., longer study reqd.	TOX complete 2/21/86. ORD verified 5/20/87.

POPULATION SUBGROUP	TOTAL TMRC (MG/KG BODY WEIGHT/DAY)	NEW TMRC AS PERCENT OF RFD	DIFFERENCE AS PERCENT OF RFD	EFFECT OF ANTICIPATED RESIDUES ARC (MG/KG/DAY)	XRFD
U.S. POPULATION - 48 STATES	0.000000	14.007333	14.007333	0.000003	1.033667
U.S. POPULATION - SPRING SEASON	0.000000	14.224333	14.224333	0.000003	0.963333
U.S. POPULATION - SUMMER SEASON	0.000000	14.381667	14.381667	0.000003	1.022000
U.S. POPULATION - FALL SEASON	0.000000	13.519333	13.519333	0.000003	0.924333
U.S. POPULATION - WINTER SEASON	0.000000	13.905000	13.905000	0.000004	1.201667
NORTHEAST REGION	0.000000	13.802333	13.802333	0.000004	1.207333
NORTH CENTRAL REGION	0.000000	14.619333	14.619333	0.000003	0.943000
SOUTHERN REGION	0.000000	13.990333	13.990333	0.000003	0.836000
WESTERN REGION	0.000000	13.416667	13.416667	0.000004	1.272000
HISPANICS	0.000000	12.923667	12.923667	0.000003	0.942667
NON-HISPANIC WHITES	0.000000	14.042667	14.042667	0.000003	1.049667
NON-HISPANIC BLACKS	0.000000	14.154667	14.154667	0.000003	0.876667
NON-HISPANICS OTHER	0.000000	15.226667	15.226667	0.000006	1.906333
MURSING INFANTS (<1 YEAR OLD)	0.000000	6.395667	6.395667	0.000003	0.982333
NON-MURSING INFANTS (<1 YEAR OLD)	0.000000	22.359000	22.359000	0.000013	4.284000
FEMALES (13+ YEARS, PREGNANT)	0.000000	10.422667	10.422667	0.000003	0.927333
FEMALES 13+ YEARS, MURSING	0.000000	10.518333	10.518333	0.000001	0.361667
CHILDREN (1-6 YEARS OLD)	0.000000	35.592333	35.592333	0.000009	3.104667
CHILDREN (7-12 YEARS OLD)	0.000000	23.849333	23.849333	0.000005	1.589000
MALES (13-19 YEARS OLD)	0.000000	15.147333	15.147333	0.000002	0.652667
FEMALES (13-19 YEARS OLD, NOT PREG. OR MURSING)	0.000000	13.649667	13.649667	0.000002	0.671333
MALES (20 YEARS AND OLDER)	0.000000	9.357333	9.357333	0.000002	0.611000
FEMALES (20 YEARS AND OLDER)	0.000000	8.788333	8.788333	0.000002	0.659667

\*Current TMRC does not include new or pending tolerances.  
 \*\*New TMRC includes new, pending, and published tolerances.

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FOOD CODE	FOOD	FOOD FORM	PET.#	TOLERANCE (ppm)	ANTICIPATED RESIDUE (ppm)	AR TYPE	% CROP TREATED	RES. VALUE USED IN TAS RUN (ppm)
06013AA	PINEAPPLE-PULP	10 RAW-FRESH OR NFS	2F2609	M 0.050000	0.050000		50.00	0.025000
06013AA	PINEAPPLE-PULP	21 COOKED-NFS	2F2609	M 0.050000	0.050000		50.00	0.025000
06013AA	PINEAPPLE-PULP	31 COOKED-FRESH OR CANNED	2F2609	M 0.050000	0.050000		50.00	0.025000
06013DA	PINEAPPLE-DRIED	10 RAW-FRESH OR NFS	2F2609	M 0.050000	0.050000		50.00	0.025000
06013JA	PINEAPPLE-JUICE	10 RAW-FRESH OR NFS	2F2609	M 0.050000	0.050000		50.00	0.025000
06013JA	PINEAPPLE-JUICE	15 RAW-FRESH OR CANNED	2F2609	M 0.050000	0.050000		50.00	0.025000
06013JA	PINEAPPLE-JUICE	21 COOKED-NFS	2F2609	M 0.050000	0.050000		50.00	0.025000
06013JA	PINEAPPLE-JUICE	31 COOKED-FRESH OR CANNED	2F2609	M 0.050000	0.050000		50.00	0.025000
25003SA	CANE SUGAR	10 RAW-FRESH OR NFS	2F2609	M 0.050000	0.050000		2.00	0.001000
25003SA	CANE SUGAR	21 COOKED-NFS	2F2609	M 0.050000	0.050000		2.00	0.001000
25003SA	CANE SUGAR	22 COOKED-FRESH-BAKED	2F2609	M 0.050000	0.050000		2.00	0.001000
25003SA	CANE SUGAR	31 COOKED-FRESH OR CANNED	2F2609	M 0.050000	0.050000		2.00	0.001000
25003SB	SUGAR-MOLASSES	10 RAW-FRESH OR NFS	2F2609	M 0.050000	0.050000		2.00	0.001000
25003SB	SUGAR-MOLASSES	21 COOKED-NFS	2F2609	M 0.050000	0.050000		2.00	0.001000
25003SB	SUGAR-MOLASSES	22 COOKED-FRESH-BAKED	2F2609	M 0.050000	0.050000		2.00	0.001000
25003SB	SUGAR-MOLASSES	31 COOKED-FRESH OR CANNED	2F2609	M 0.050000	0.050000		2.00	0.001000

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COMMODITY CONTRIBUTION BY RAC FOR: U.S. POPULATION - 48 STATES

FOOD CODE	FOODNAME/FOODFORM	TOLERANCE (PPM)	TYPE	TMRC (UG/KG/DAY)	XRFD	ANTICIPATED RESIDUE (PPM)	ARC (UG/KG/DAY)	XRFD
06013AA	PINEAPPLE-FRESH,PULP 10 RAW-FRESH OR NFS 21 COOKED-NFS 31 COOKED-FRESH OR CANNED	0.050000	N	0.001541	0.513667	0.025000	0.000279	0.093000
060130A	PINEAPPLE-DRIED 10 RAW-FRESH OR NFS PINEAPPLE-FRESH,JUICE 10 RAW-FRESH OR NFS 15 RAW-FRESH OR CANNED 21 COOKED-NFS 31 COOKED-FRESH OR CANNED	0.050000	N	0.000006	0.002000	0.025000	0.000472	0.157333
06013JA	PINEAPPLE-FRESH,JUICE 10 RAW-FRESH OR NFS 15 RAW-FRESH OR CANNED 21 COOKED-NFS 31 COOKED-FRESH OR CANNED	0.050000	N	0.003161	1.053667	0.025000	0.000027	0.009000
25003SA	CANE SUGAR 10 RAW-FRESH OR NFS 21 COOKED-NFS 22 COOKED-FRESH-BAKED 31 COOKED-FRESH OR CANNED	0.050000	N	0.036788	12.262667	0.025000	0.000750	0.243333
25003SB	SUGAR-MOLASSES 10 RAW-FRESH OR NFS 21 COOKED-NFS 22 COOKED-FRESH-BAKED 31 COOKED-FRESH OR CANNED	0.050000	N	0.000526	0.175333	0.001000	0.000125	0.041667
<b>CROP GROUP TOTALS FOR UNSPECIFIED:</b>					<b>14.007333</b>	<b>0.001000</b>	<b>0.000337</b>	<b>0.112333</b>
					<b>0.042022</b>	<b>0.001000</b>	<b>0.000000</b>	<b>0.028000</b>
					<b>0.003101</b>	<b>0.001000</b>	<b>0.000003</b>	<b>0.063333</b>
					<b>1.033667</b>	<b>0.001000</b>	<b>0.000006</b>	<b>0.041667</b>
					<b>1.033667</b>	<b>0.001000</b>	<b>0.000002</b>	<b>0.112333</b>

TOLERANCE TYPE: N=NEW; A=PENDING; P=PUBLISHED  
 TMRC=THEORETICAL MAXIMUM RESIDUE CONTRIBUTION  
 ARC = ANTICIPATED RESIDUE CONTRIBUTION  
 RFD = REFERENCE DOSE